Influence of Ion Pairing, Steric Effects, and Other Specific Interactions on the Reactivity of Thioanions with Chloronitrobenzenes. Nucleophilic Aromatic Substitution vs Reduction

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The reactions in 2-propanol of the isomeric chloronitrobenzenes with thiolate nucleophiles, RS^- (R = Me, *i*-Pr, *t*-Bu, Ph), have been studied to test for the ability of these representative thioanions of inducing chloride displacement and/or nitro reduction. *m*-Chloronitrobenzene gives a complex mixture of products, all still retaining the chlorine substituent, via redox processes involving nitro reduction and ring alkylthiolation. In contrast, the ortho and para isomers undergo substitution of chloride according to the addition/elimination S_NAr mechanism also when O_2 is removed from the reaction environment. Notably, treatment of *o*- and *p*-chloronitrobenzene with the oxanion 2-propoxide in oxygen-free *i*-PrOH results, instead, in nitro reduction. Kinetic and product studies indicate that *i*-PrS^- is more reactive than *i*-PrO^- in both redox and S_NAr reactions, the difference in reactivity being, however, considerably greater in the latter process. The $MeS^- > i\text{-}PrS^- > PhS^- > t\text{-}BuS^-$ reactivity order observed in the S_NAr reactions is opposite, as far as the aliphatic thiolates are concerned, to the order of basicity. Notably, reactivity drops with increasing bulkiness of the attacking nucleophile. However, kinetic results obtained under conditions of ion paired and of "free" anions and the effects of ion pairing on the k_{ortho}/k_{para} ratios suggest that steric effects in the transition states are scarcely dependent on the bulkiness of the substituent R in the nucleophile RS^- and that nucleophilic reactivity is largely determined by the extent of charge concentration on the attacking atom, which, in turn, affects the strength of ion-pairing interactions.

Thioanions are powerful reagents both as nucleophiles toward electrophilic carbon in substitution reactions[1] and as reducing agents in radical processes.[2] It was early noted that in nucleophilic displacement reactions sulfur nucleophiles are generally "much more reactive than would be expected from their basicity".[3] Particularly striking is the comparison between S and O anions, the former being weaker bases but far superior reagents in nucleophilic substitution both on aliphatic and aromatic substrates. Thus, while 4-nitrothiophenoxide is less basic than 4-nitrophenoxide (ΔpK_a is 2.43 in water),[4] its S_N2 reaction with CH_3I in CH_3OH is 4 orders of magnitude faster.[5] It was later shown that when anions of equal basicity are compared, their nucleophilic reactivity follows the order $S^- \gg C^- > O^- > N^-$.[6] This "donor-atom effect" appears to be quite general and applies to S_N2[6] as well as S_NAr[7] reactions. The abnormally high reactivity of sulfur nucleophiles has intrigued chemists for a long time and inspired much work aimed at defining nucleophilicity scales and at rationalizing reactivity data through correlations with such parameters as reactants polarizability.[8]

Once "intrinsic" basicity and reactivity data become available from equilibria and kinetic experimental determinations in the gas phase, the enormous impact of solvation on solution reactivity could be fully realized and used in rationalizing certain observed patterns.[9-11] Specifically, CH_3S^- is less reactive than CH_3O^- in gas-phase S_N2 reactions, indicating that the enhanced reactivity of thioanions in solution is a solvation phenomenon due to the greater solvation of the oxanion.[10] It was shown that with anions belonging to the same "family", i.e., anions in which the donor atom is the same and structural variations occur at sites far from the reactive center, solution reactivity data correlate linearly with basicity. Thus, a good linear Brøsted correlation extending over 9 pK units was found for the reaction of ring-substituted thiophenoxide ions with *n*-BuCl in DMSO.[6] Data points for the same reaction involving aliphatic thiolates, however, fall off the line and appear to describe another line, characterized by a far greater scatter. This was ascribed to the fact that major structural changes have been made near the reacting center resulting in steric hindrance to the approach of the nucleophile and steric hindrance to solvation.[6]

Steric hindrance was also invoked as the factor determining reactivity in the reaction of RS^- anions with 2-chloro- and 2-bromobenzothiazole in alcoholic solvents.[12] Notably, in these reactions the reactivity order was $MeS^- > i\text{-}PrS^- > t\text{-}BuS^-$, which is opposite to the order of basicity in solution.[4]

The potential bivalent reactivity of thioanions mentioned earlier, i.e., as nucleophiles and as reductants, can bring about undesired complications. Thus, early attempts to perform nucleophilic aromatic substitution on nitroaromatic halides in protic solvents failed because of prevailing substrate reduction to the corresponding azoxy derivative.[13] Reduction can be inhibited and avoided, most commonly by the use of radical traps, of polar aprotic solvents, or of cation complexing agents in protic solvents.[14,15]

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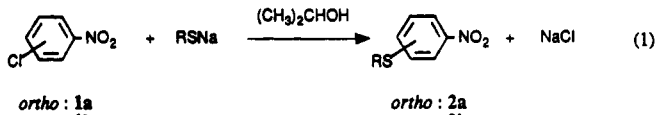
The presence of two reactive sites in nitroaryl halides, the reducible nitro group and the displaceable halogen substituent, has been exploited in previous work from our group to study the reactivity of alkoxide ions in alcohols and the factors that govern the competition between radical (nitro reduction) and ionic (halide displacement) processes.[16-20] It was found that reaction of *p*-chloronitrobenzene, a typical substrate for S_NAr substitutions, with *i*-PrOK in oxygen-free *i*-PrOH gives products of nitro reduction, mainly azoxy and anilino derivatives, via a radical process involving initial conversion to *p*-chloronitrosobenzene.[17] This behavior is not unique to *p*-chloronitrobenzene. Reduction prevails in the reaction of *i*-PrOK in oxygen-free *i*-PrOH with all halonitrobenzenes, except 2- and 4-fluoronitrobenzene, which undergo S_NAr substitution to the corresponding nitrophenyl 2-propyl ethers in quantitative yields.[18] It was also shown that ion-pairing effects have major consequences in determining reactivity in these systems.[16,18-20] Thus, alkoxydehalogenation occurs for all activated substrates (*o*- and *p*-halonitrobenzenes) when the "free" anion is employed, as observed in solutions containing the K^+ complexant 18-crown-6.[18] A detailed investigation proved that such a change in reactivity from reduction to substitution when free alkoxides are used is due not only to activation of the latter process but also to depression of the former.[16,18]

In view of these findings and of the fact that thiolates should be better one-electron donors and also better nucleophiles in displacement reactions than alkoxide ions, the extension of the investigation to some representative thioanions was of great interest. We noted that, despite the numerous reports on the superior quality of sulfur anions in nucleophilic aromatic substitutions in mechanistic studies and applications, a comprehensive and homogeneous set of data was lacking on the effect of R and of ion pairing on the reactivity of RS^- toward typical substrates for S_NAr reactions, such as *o*- and *p*-halonitrobenzenes. Moreover, the complex question of competing reduction so far has not been specifically addressed. The present investigation reports data for the reaction of a series of representative thioanions with various nitroaryl halides in a unique solvent under conditions of ion-paired and free ions. The data provide the basis for a discussion of steric and ion-pairing effects in nucleophilic aromatic substitution and for a comparison with alkoxide ions particularly as far as competition between reduction and substitution is concerned.

Results

Reaction of *o*- (**1a**) and *p*-chloronitrobenzene (**1b**) with a 10-fold excess of RSNa (R = Me, *i*-Pr, *t*-Bu, Ph) gave the thioethers **2a** and **2b**, respectively (eq 1). Yields were



(1)

ortho: **1a** *para*: **1b** *ortho*: **2a** *para*: **2b**

quantitative except for R = *t*-Bu, in which case they were in the range 67–78%. The kinetics of the reaction were also studied. The decay in time of the substrate concentration, monitored by GC quantitative analysis, followed invariably an exponential curve from which a pseudo-first-order kinetic constant, k_ψ, was derived. A summary of kinetic and product data is presented in Table I. All data were determined at 40 °C, except for the reactions with *t*-BuSNa, which are too slow for convenient determinations at this temperature. Thus, for *t*-BuSNa, activation parameters were obtained from ln k_ψ vs $1/T$ plots based on data acquired in experiments run at 50, 60, and 70 °C as reported in Table II. The k_ψ values reported in Table I for reactions of this nucleophile were thus extrapolated at 40 °C from the activation parameters.

Table I. Kinetic and Product Data for the Reaction of *o*- and *p*-Chloronitrobenzene (9.4×10^{-3} M) with RSNa (9.4×10^{-2} M) in 2-Propanol at 40 °C

	chloronitrobenzene			
	ortho isomer, **1a**		para isomer, **1b**	
RSNa, –R	$k_\psi \times 10^3$, s^{-1}	**2a**, % yield	$k_\psi \times 10^3$, s^{-1}	**2b**, % yield
CH_3	0.778	>95	1.09	>97
$CH(CH_3)_2$	0.231	>95	0.241	>96
$C(CH_3)_3$	0.0383[a]	70, 68, 67[b]	0.0159[a]	78, 73, 68[b]
C_6H_5	0.098	>95	0.159	>96

[a] Extrapolated from data obtained at higher temperatures (see Table II). [b] Data for experiments conducted at 50, 60, and 70 °C, respectively.

Table II. Kinetic Data and Activation Parameters for the Reaction of *o*- and *p*-Chloronitrobenzene (9.4×10^{-3} M) with *t*-BuSNa (0.094 M) in 2-Propanol

$10^4 \times k_\psi$, s^{-1}	T, °C			E_a, kcal mol^{-1}	$10^{-9} \times A$, s^{-1}
	50	60	70		
ortho (**1a**)	0.99	2.40	5.80	19.5	1.60
para (**1b**)	0.41	1.07	2.48	19.9	1.15

It was also observed that *o*- and *p*-fluoronitrobenzene undergo the substitution reaction more readily than the corresponding chloro derivatives. Thus, for example, *p*-fluoronitrobenzene was converted quantitatively to **2b** (R = Me) in less than 30 min at room temperature, whereas reaction of *p*-chloronitrobenzene required 1.5 h at 40 °C.

In order to establish the kinetic order for the substitution reaction of eq 1 with respect to the nucleophile, a series of experiments was performed in which the substrate concentration was maintained the same (3.0×10^{-3} M) and the nucleophile concentration was changed within the range 0.03–0.10 M (pseudo-first-order conditions). The reaction of 4-chloronitrobenzene with *i*-PrSNa in *i*-PrOH at 40 °C was chosen as model for this study. k_ψ values of 0.67×10^{-4}, 1.42×10^{-4}, and 2.34×10^{-4} s^{-1} were obtained for concentrations of *i*-PrSNa of 3.06×10^{-2}, 6.05×10^{-2}, and 9.02×10^{-2} M, respectively. The plot of ln k_ψ vs ln [*i*-PrSNa] is linear with a slope equal to 1.15 ± 0.04, which, according to the expression $k_\psi = k[\text{nucleophile}]^n$, corresponds to the kinetic order in nucleophile.

The reactions with *t*-BuSNa received special attention since the yield of substitution products after complete conversion of the substrate never exceeded 70 and 78% for the ortho and para isomers, respectively. The stability of the products under typical reaction conditions was tested first. 4-Nitrophenyl *tert*-butyl sulfide (**2b**) remained largely unreacted after treatment with a 10-fold excess of *t*-BuSNa in 2-propanol for 22 h at 70 °C, the corresponding anilino derivative, 4-aminophenyl *tert*-butyl sulfide being the only other component detectable in traces by GC–MS analysis. Thus, the low yields of reaction 1 in the case R = *t*-Bu are not due to the instability of the products but to the operation of competitive substrate-consuming pro-

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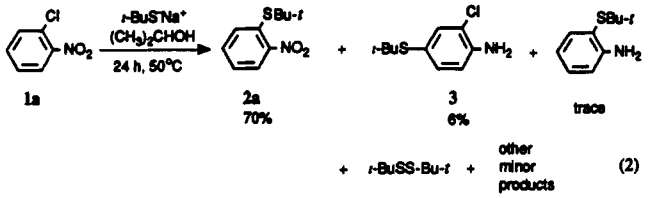
Table III. Kinetic Data for the Reaction of *o*- and *p*-Chloronitrobenzene (9.4×10^{-3} M) with RSNa (9.4×10^{-2} M) in 2-Propanol in the Presence of 18-Crown-6 (0.12 M)

Cl, NO_2	-R	T, °C	$k_\psi^{crown} \times 10^3$, s^{-1}	k_ψ^{crown}/k_ψ
ortho (1a)	$C(CH_3)_3$	50	0.16	1.62
para (1b)	$C(CH_3)_3$	50	0.64	15.6
ortho (1a)	CH_3	40	1.56	2.00
para (1b)	CH_3	40	7.19	6.60

cesses. GC–MS analysis of a concentrated solution of the crude reaction mixture revealed the presence of several minor peaks with mass spectra indicating the presence of the amino functionality. The major of these products (eq 2) was isolated in pure form by column chromatography and characterized as 3-chloro-4-aminophenyl *tert*-butyl sulfide, **3** (6% yield). The occurrence of anilino derivatives indicates that with *t*-BuSNa a minor component of nitro reduction takes place also in nondeoxygenated solutions.

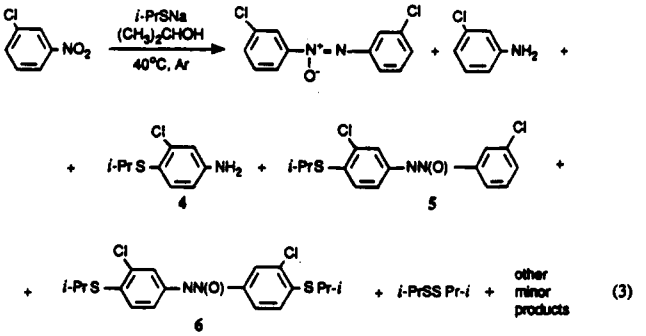


Control experiments indicated that rates and yields of reaction 1 were not significantly affected when O_2 was excluded from the reaction environment. The only results worth mentioning with this regard concern the reactions with MeSNa, which, under argon, are slightly faster (e.g., k_ψ for the reaction of **1a** is 0.84×10^{-3} s^{-1} under argon and 0.78×10^{-3} s^{-1} under air) and the slow decay in time of the concentration of **2b** (R = *t*-Bu) under argon, not detectable in reactions conducted under air, likely due to reduction of the nitro functionality (see above).

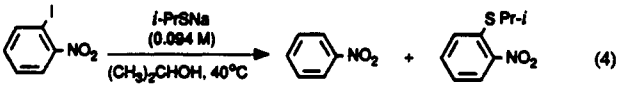
The effects of ion pairing were examined next. To this end experiments were conducted for the two extreme cases, R = *t*-Bu and R = Me, with 18-crown-6 present in ca. 30% excess with respect to RSNa. Under these conditions the sodium cation is complexed quantitatively.[21] A summary of the results is presented in Table III.

The possibility was taken into consideration that reaction 1 proceeds according to the radical-chain mechanism $S_{RN}1$,[22] since sulfur anions are among the most efficient nucleophiles in these reactions. An $S_{RN}1$ reaction appeared, however, rather unlikely in the present systems since nitro-substituted aryl halides are not useful substrates in the $S_{RN}1$ reaction[22] because of the stability of their radical anions.[23] Moreover, oxygen has no effect on reaction 1. Additional evidence was sought by examination of two models, *m*-chloronitrobenzene and *o*-iodonitrobenzene. The former is not activated for nucleophilic displacement via the addition/elimination S_NAr reaction, while in a hypothetical $S_{RN}1$-type substitution it could possibly react with a rate not largely different from that of its ortho and para isomers. Thus, the three isomers of chloroiodobenzene react with PhS^- under photostimulation (typical $S_{RN}1$ conditions) to give after similar reaction times the corresponding *o*-, *m*-, and *p*-bis(thiophenoxy)-benzenes in high yields.[24] The latter, *o*-iodonitrobenzene, is the only nitro-substituted aryl halide known so far to undergo the $S_{RN}1$ reaction,[25] due to the relatively high rate of fragmentation of its radical anion to aryl radical and I^-.[26]

The reaction of *m*-chloronitrobenzene with *i*-PrSNa gave no product of Cl substitution, but a complex mixture of products resulting from nitro reduction and ring oxidation, as exemplified by eq 3. Closely related redox processes are known to proceed via the intermediacy of the substrate radical anion.[16,18]



The reaction of *o*-iodonitrobenzene with the same nucleophile produced nitrobenzene and the product of iodine substitution **2a** in relative amounts that were somewhat affected by the presence of oxygen, as indicated in eq 4.



air:	34.5%	67.4%
argon:	39.5%	59.0%

Discussion

Concerning the mechanism of the substitution process, at least four alternatives should be considered in principle: the addition/elimination (S_NAr),[27] the radical chain ($S_{RN}1$),[22] the elimination/addition (benzyne), and the S_N1 reactions. The last two, which require, respectively, very strongly basic conditions and excellent leaving groups, can be reasonably dismissed as highly unlikely. In view of the reported ability of thioanions to transfer one electron to nitroaromatic compounds[2,28,29] and of their efficiency as nucleophiles in aromatic $S_{RN}1$ substitutions,[22] the possibility was carefully considered that reaction 1 proceeds via this radical-chain mechanism, the propagation cycle of which is shown in Scheme I.

Scheme I

$$[ArX]^{\bullet-} \rightarrow Ar^\bullet + X^-$$

$$Ar^\bullet + Y^- \rightarrow [ArY]^{\bullet-}$$

$$[ArY]^{\bullet-} + ArX \rightarrow ArY + [ArX]^{\bullet-}$$

This alternative, however, is rejected on the basis of the following considerations. First, O_2, a powerful oxidant of arene radical anions,[30,16,17,18] has no effect on the rate of

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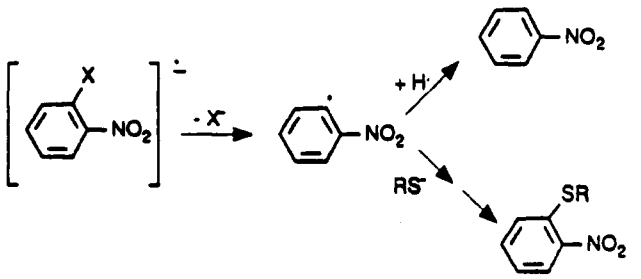
Scheme II



reaction 1. Second, nitro substituents characteristically interfere with the $S_{RN}1$ reaction.[22] Third, the product distributions obtained with *o*-chloro- and *o*-iodonitrobenzene are conspicuously different. While the former gives the thioethers **2a** in quantitative yields (eq 1), the latter also produces large amounts of nitrobenzene (eq 4) via I^- loss from the substrate radical anion and H abstraction by the *o*-nitrophenyl radical.[18,31] Under the hypothesis that substitution proceeds via the $S_{RN}1$ mechanism, the same intermediate, *o*-nitrophenyl radical, should be produced from both *o*-chloro- and *o*-iodonitrobenzene. This species should then react in a manner that is independent of the halogen substituent originally present in the precursor molecule, according to the pattern indicated in Scheme II. Since this is not the case, the intermediacy of aryl radicals in the reactions of *o*-chloronitrobenzene and, for a logical extension, of its para isomer is rejected. As for *o*-iodonitrobenzene, the reaction can possibly follow Scheme I, or alternatively, involve two parallel routes, one radical leading to nitrobenzene, the other leading to substitution via the addition/elimination sequence of the S_NAr mechanism.[32] The effect of oxygen on product partitioning (eq 4) perhaps render this latter possibility more likely.

All the available data for reaction 1 is consistent with the S_NAr mechanism with addition of the nucleophile being rate limiting. Specifically, the reaction is kinetically of the first order both with regard to the substrate and to the nucleophile (the slight deviation from unity of the latter is discussed later), it is insensitive to the presence of O_2, and it displays characteristic leaving group (F better than Cl) and positional (ortho, para ≫ meta) effects. Some closely related reactions of halonitrobenzenes with thiolates in alcoholic solvents obey to the same mechanistic criteria and are bona fide examples of the S_NAr reaction.[8,12,27,35]

The fact that *m*-chloronitrobenzene does not undergo the substitution reaction of eq 1 is in keeping with the reactivity pattern typical of the addition/elimination (S_NAr) reaction.[27] Products of nitro reduction are observed instead (eq 3), which indicate that the substrate radical anion forms but, in contrast to the behavior of *o*-iodonitrobenzene, does not undergo dehalogenation via fragmentation. This finding is consistent with the known relative stability toward fragmentation of nitroaryl halides, *o*-I ≪ *o*-Cl < *p*-Cl < *m*-Cl.[26]

The data of reaction 1 can now be examined and discussed within the framework of the S_NAr mechanism, with specific regard to the effects of substrate and nucleophile structures and of ion-pairing phenomena. For this purpose, relative reactivity data have been calculated (Table IV) from the data of Tables I and III.

Table IV. Relative Reactivity Data of *o*- and *p*-Chloronitrobenzenes with RSNa in 2-Propanol[a]

-R	ortho isomer	para isomer	k_{ortho}/k_{para}	$k_{ortho}^{crown}/k_{para}^{crown}$
CH_3	20.3	68.6	0.72	0.22
$CH(CH_3)_2$	6.0	15.6	0.96	
$C(CH_3)_3$	(1.00)	(1.00)	2.41	0.25[b]
C_6H_5	2.6	10.0	0.62	

[a] Data taken at 40 °C, unless otherwise specified. [b] Data taken at 50 °C.

It is seen that the same qualitative reactivity order is found for *o*- and *p*-chloronitrobenzene, i.e., MeSNa > *i*-PrSNa > PhSNa > *t*-BuSNa. Interestingly, we observe that kinetic reactivity decreases with increasing proton basicity of the nucleophile (pK_a^{RSH} in H_2O: MeSH (10.33), *i*-PrSH (10.86), *t*-BuSH (11.22), and PhSH (6.61)).[4] In fact, for the alkyl thiolates the order of reactivity is *opposite* to that of basicity. The reactivity scale observed in the present study in the same, as far as the alkylthiolates are concerned, as that previously found for Cl substitution in 2-chlorobenzothiazole in MeOH, for which relative rates were MeS^- (79), $i\text{-}PrS^-$ (13), and $t\text{-}BuS^-$ (1.00), respectively.[12] The explanation offered for the observed trend was that reactivity is governed by steric factors and decreases with increasing bulkiness of R in the nucleophile RS^-.[12] A similar reasoning could at first inspection explain the present data. However, from the data of Table IV it appears that attack at the position ortho to the nitro group is less sensitive to steric hindrance than attack at the position para. Indeed, the reactivity range spanned within the series MeSNa, *i*-PrSNa, *t*-BuSNa, is 1–69 for *p*- and 1–20 for *o*-chloronitrobenzene, respectively. Since steric effects should reasonably be more stringent for attack at the ortho position the explanation based solely on steric effects is insufficient to account for the results of the present investigation. Particularly difficult to explain on this basis is the fact that the ortho isomer (**1a**) is 2.3 times more reactive than the para (**1b**) with the bulkiest nucleophile, *t*-BuSNa, while with MeSNa the ratio of k_{ortho}/k_{para} is 0.71. Notably, k_{para} is normally greater than k_{ortho} in reactions of halonitrobenzenes with anionic nucleophiles.[27b] We believe that anion/cation interactions play a major role in determining reactivity.

The results obtained in the presence of the cation complexing agent 18-crown-6 are very informative with this regard. It is known that 2-propanol, a solvent of low ionizing power, favors aggregation of its lyate salts into ion pairs and/or higher aggregates.[33] The addition of cation complexing agents causes disruption of ion pairs and results in the activation of the nucleophile reactivity. Thus, it was shown that the rate of nucleophilic aromatic substitution of Cl in *p*-chloronitrobenzene with *i*-PrOK in 2-propanol is inversely dependent on the degree of ion pairing.[18] Although no data are available, it is reasonably assumed that, in analogy to what found for alkali alkoxides, ion pairing occurs extensively in 2-propanol solutions of the sodium thiolates (evidence has been reported that PhSK is largely present as ion pairs in *t*-BuOH[35]). Consistent with this assumption is the observation that addition of 18-crown-6 causes a considerable rate increase in the reaction of **1b** both with MeSNa and with *t*-BuSNa (Table III), which is attributed to an increase in the reactivity of the nucleophile due to loss of solvation by the cation. Similar effects are observed for **1a**, although in this

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case rate accelerations are much smaller. This type of ortho effect has precedents in the literature and is explained as follows.[34,35,18] Removal of the cation by complexation causes the loss of the specific stabilizing interaction due to bridging of the cation between the nucleophile and the oxygens of the nitro group. This effect opposes the one of activation of the anion nucleophilicity discussed above:[18,19] the net kinetic result depends in each specific case by the relative weight of these opposing effects.

It is worth emphasizing that although the data demonstrate the occurrence of ion pairing, they do not provide direct information about the extent of association in ion pairs and/or higher aggregates. The kinetic order of 1.15 determined with respect to the nucleophile for the reaction without the complexing agent indicates that the observed rate constant increases with concentration of the nucleophile. This phenomenon can be due to salt effects and/or to variable degrees of aggregation of the nucleophile RSNa depending on its concentration. One possible interpretation suggests that the reactivity of the anion in higher aggregates is slightly enhanced with respect to that of the ion-paired species. This phenomenon has been observed previously[36] but is not general.[37]

Ion-pairing phenomena can also account for the observed dependence of the k_{ortho}/k_{para} ratio on the group R in the nucleophile RSNa (Table IV). A tentative explanation is based on the consideration that, plausibly, the inductive effect of the substituent R creates a more and more concentrated charge on sulfur as R is changed from Me to *i*-Pr and to *t*-Bu. To this increase in charge density on the sulfur atom should reasonably correspond an increase in the association constant with the counterion Na^+. Thus, *t*-BuSNa should be more strongly associated than MeSNa. A stronger association with the cation is expected to cause a slower rate of attack onto the para position (a "normal" effect). For attack at the ortho position, on the other hand, greater association with the cation should provide a stronger stabilization of the transition state (the ortho effect described above). Both effects contribute in increasing the k_{ortho}/k_{para} ratio in going from *t*-BuSNa to MeSNa. Support to this interpretation is provided by the values of the k_ψ^{crown}/k_ψ for *p*-chloronitrobenzene to be found in Table III. The considerably larger value determined with *t*-BuSNa (15.6) than with MeSNa (6.6) is plausibly due to a greater degree of association with the cation in the case of the *t*-BuS^- anion.

Following the previous considerations, the role played by the bulkiness of the R group in determining the reactivity of RSNa reagents can now be discussed with greater insight. The data show that in the presence of complexed cation, i.e., under conditions of minimal specific anion/cation interactions, *p*-chloronitrobenzene is ca. 4 times more reactive than *o*-chloronitrobenzene both with *t*-BuS^- and with MeS^- ($[k_{ortho}/k_{para}]^{crown}$ is 0.25 and 0.22 for *t*-BuS^- and MeS^-, respectively). These data suggest that in the absence of specific interactions with the cation, attack of the nucleophile is less favored to the ortho than to the para position by a factor that is independent of the bulkiness of R in RS^-. It is thus concluded that the transition state for attack of the nucleophile to the ortho position suffers from steric effects due primarily to interaction of the nitro group with the sulfur atom, but not significantly with the remote substituent R. This lack of sensitivity to structural variation in the substituent R is probably to be attributed to the size of the sulfur atom and the length of the C---S incipient bond.

The data relative to benzenethiolate were not included in the preceding discussion, since this anion belongs to a different "family" of bases.[6] Benzenethiolate has a remarkably high reactivity considering its low basicity (pK_a in H_2O is 6.5). Delocalization of the charge by resonance is certainly an important factor and, possibly, could cause a considerable relaxation in the interaction with the cation.

In keeping with the generally observed superiority of sulfur relative to oxygen anions in nucleophilic aromatic substitution we find that the reaction of *p*-chloronitrobenzene in *i*-PrOH with *i*-PrSNa at 40 °C is ca. 50 times faster than with *i*-PrOK at 75 °C.[16]

Finally, some comments are pertinent on the ability of the sulfur anions to induce nitro reduction. Also in this type of process the thioanion appears to be more efficient than the corresponding oxanion, although less so than in the S_NAr reaction. Thus, the rates of *m*-chloronitrobenzene reduction in oxygen-free *i*-PrOH with *i*-PrSNa at 40 °C and with *i*-PrOK at 75 °C[18] are about equal. Notably, chloride displacement takes place with all RSNa used in this study also under anaerobic conditions, the only exception being the minor component of reduction observed with *t*-BuSNa. In contrast, with *i*-PrOK in oxygen-free *i*-PrOH solutions *o*- and *p*-chloronitrobenzene give exclusively the products of nitro reduction.[18] It should be also pointed out that the thiolate–induced reduction of *m*-chloronitrobenzene produces a more complex mixture of products (eq 3) than the analogous alkoxide-induced reaction. It also gives a greater fraction of anilino relative to azoxy derivatives and considerable amounts of products of nitro reduction in which ring alkylthiolation has occurred. The reduction process is currently under investigation in our laboratories.

Summary and Conclusions

The results of the present investigation strongly support the concept that electrostatic interactions with the counterion are of major consequence in determining reactivity of anionic nucleophiles in S_NAr reactions, as revealed by absolute rates and by the k_{ortho}/k_{para} ratio.[19,34,35,38] Differential steric inhibition to solvation of the transition states for attack in ortho and in para was proposed in earlier studies as the cause for the variance of the k_{ortho}/k_{para} ratio in reactions with RO^- in ROH.[39] This proposal is, however, inadequate to account for all the experimental observations of the present study.

The role played by the cation in determining the reactivity of anionic nucleophiles in solvents of low polarity is rapidly gaining recognition. Removal of the cation by complexation can have different consequences on the rate of S_NAr reactions depending on which is the rate-limiting step and whether the leaving group is ortho to the activating NO_2 substituent. When addition of the nucleophile is rate limiting, as in the systems here described, two effects, which contrast each other, must be considered. The first, quite general, is activation of the nucleophile and results in enhanced reactivity. The second, specific for ortho derivatives, is loss of the stabilizing electrostatic interaction between the bridged cation and the delocalized negative charge in the transition state and results in depressed reactivity. When the second step is rate limiting

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(elimination), removal of the cation causes a drop in the reactivity of ortho isomers because the "cooperative" effect is lost that facilitates departure of the leaving group.[38]

The use of a common solvent of low polarity, 2-propanol, and of structurally different thiolates allowed us to compare reactivities under strictly homogeneous conditions. The analysis of steric effects and ion-pairing effects suggests that the bulkiness of the substituent R in the nucleophile RS^- has no major effect in determining the ortho/para reactivity ratio, i.e., steric effects are greater for attack in ortho than in para but this difference is irrespective of the substituent R. An analogous analysis is not possible for alkoxides since each can be studied only in the parent alcohol. Thus, only overall effects which include strong solvent effects, can be obtained.[20]

Experimental Section

GC analyses were performed on a Varian 3700 gas chromatograph interfaced to a Shimadzu Chromatopac C-R4A integrator. A Hewlett-Packard 5890 GC5970 MSD system interfaced to a HP 59940A MS Chemstation was used for GC–MS analysis, with a 15-m fused silica column of polymethylsiloxane bonded phase. ^{1}H NMR spectra were recorded on a 200-MHz Bruker spectrometer. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-2f mass spectrometer.

Materials. Reagent-grade 2-propanol was fractionally distilled from Mg turnings. The halonitrobenzenes were commercial samples (Aldrich and Merck) purified by recrystallization from EtOH. The RSNa salts (R = Me, *i*-Pr, *t*-Bu) were the products of Fluka and were used as received. PhSNa was prepared in situ by the addition of PhSH to a solution of *i*-PrONa in *i*-PrOH prepared from Na and freshly distilled *i*-PrOH. 18-Crown-6 (Fluka) was vacuum dried prior to use. Linear-chain hydrocarbons used as internal standards in GC analysis were the GC standards products of Carlo Erba.

Kinetic Studies. The apparatus and procedures were as previously described,[18] with the following minor modifications in the treatment of reaction aliquots prior to GC analysis. Each aliquot was transferred into a 1-mL centrifuge tube containing a small chunk of dry ice, diluted with Et_2O, and centrifuged until a clear solution was obtained (15 000 rpm for 10 min). For solutions containing 18-crown-6, two successive extractions of the organic layer were performed with aqueous saturated KCl in order to remove the cyclic ether prior to GC analysis of each aliquot. Several control experiments indicated that reproducibility in the determination of k_ψ values was within a few points percent.

Product Studies. Product studies were carried out under the same conditions used for kinetic experiments. The general procedure for workup and product isolation was as follows. The reaction mixture was poured in dilute aqueous HCl (2%) and extracted three times with Et_2O. The products were isolated from the crude organic extracts by low-pressure column chromatography (Kieselgel 60; o.d. 0.015–0.040 mm from Merck) and, whenever possible, recrystallized from an appropriate solvent. All products gave analytical and spectral data in good agreement with literature values and with the structural assignment. For new compounds, combustion analysis and/or HRMS data were obtained. The purity was >95% as determined by ^{1}H NMR.

o-Nitrophenyl thioethers (**2a**): R = Me;[14e] R = *i*-Pr[14b] (oil; HRMS 197.0543, calcd 197.0508; ^{1}H NMR ($CDCl_3$) 1.40 (d, 6 H), 3.59 (sept, 1 H), 7.20–8.20 (m, 4 H); MS *m/e* 197 ($M^{\cdot+}$, 15), 182 (3), 155 (60), 138 (66), 91 (100), 43 (48), 41 (35)); R = *t*-Bu (compound not reported in the literature; oil; HRMS 211.0623, calcd 211.0666; ^{1}H NMR ($CDCl_3$) 1.31 (s, 9 H), 7.44–7.74 (m, 4 H); MS *m/e* 211 ($M^{\cdot+}$, <1), 155 (33), 138 (12), 91 (23), 57 (100), 41 (43). Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63. Found: C, 56.93; H, 6.27; N, 6.59.); R = Ph.[14a] *p*-Nitrophenyl thioethers (**2b**): R = Me;[14d] R = *i*-Pr;[14b] R = *t*-Bu;[40] R = Ph.[14b]

1-Amino-2-chloro-4-[(1,1-dimethylethyl)thio]benzene (3), a minor product in the reaction of *o*-chloronitrobenzene (0.295 g, 1.87 mmol) with *t*-BuSNa (2.10 g, 18.7 mmol), was isolated from column chromatography (eluant petroleum ether/toluene (8:2); 24.2 mg, 6%): mp 74–76 °C; ^{1}H NMR ($CDCl_3$) 1.25 (s, 9 H), 6.70 (d, 1 H, *J* = 7.93 Hz), 7.21 (dd, 1 H, *J* = 7.93, 1.83 Hz), 7.42 (d, 1 H, *J* = 1.83 Hz); MS *m/e* 215, 217 (15), 159, 161 (100), 124 (36), 114 (7), 57 (21); HRMS found 215.0544, calcd 215.0535.

Reduction of *m*-Chloronitrobenzene with *i*-PrSNa (Eq 3). The reaction was conducted under an atmosphere of argon using the equipment and the procedures previously described,[18] with 0.147 g (0.93 mmol) of *m*-chloronitrobenzene and 0.918 g (9.4 mmol) of *i*-PrSNa in 100 mL of distilled *i*-PrOH. After complete substrate consumption (20 h at 40 °C), the reaction mixture was poured in dilute aqueous HCl (2%, 100 mL) and extracted with Et_2O (3 × 150 mL). After drying over $MgSO_4$ and removal of the solvent under reduced pressure, the combined organic extracts were chromatographed (eluant petroleum ether/ethyl acetate (8:2) for the first four components, pure ethyl acetate for the last eluted component). Fractions of pure products were isolated in the following order: **3,3′-dichloroazoxybenzene,** 18.8 mg (15%), mp 97 °C[18]; **3-chloroaniline,** 22.7 mg (19%); **3,3′-dichloro-4-[(1-methylethyl)thio]azoxybenzene (5,** unresolved mixture of isomers), 9.6 mg (6%) (^{1}H NMR ($CDCl_3$) 1.43 (d, 6 H), 1.45 (d, 6 H), 3.17 (sept, 2 H), 7.35–7.59 (m, 7 H), 7.96–8.40 (m, 7 H); MS *m/e* 340 ($M^{\cdot+}$, 78), 324 (10), 298 (31), 281 (6), 270 (4), 185 (11), 157 (22), 111 (100), 75 (21), 43 (38); HRMS found 340.0244, calcd 340.0203); CAUTION: an explosion occurred during recrystallization of a small sample (few mg) of **5** from methanol; **3,3′-dichloro-4,4′-bis[(1-methylethyl)thio]azoxybenzene (6),** 15.6 mg (8%), mp 122 °C (^{1}H NMR ($CDCl_3$) 1.42 (d, 6 H, *J* = 6.5 Hz), 1.425 (d, 6 H, *J* = 6.5 Hz), 3.61 (sept, 2 H, *J* = 6.5 Hz), 7.37 (d, 2 H, *J* = 9.0 Hz), 8.07 (dd, 2 H, *J* = 9.0, 2.0 Hz), 8.14 (dd, 2 H, *J* = 9.0, 2.0 Hz), 8.32 (d, 1 H, *J* = 2.0 Hz), 8.36 (d, 1 H, *J* = 2.0 Hz); MS *m/e* 414 ($M^{\cdot+}$, 39) 398 (65), 372 (6), 355 (9), 185 (64), 173 (39), 157 (17), 143 (52), 108 (33), 43 (100)); **4-amino-2-chloro-1-[(1-methylethyl)thio]benzene (4),** oil, 52.8 mg (28%) (^{1}H NMR (CD_3OD) 1.27 (d, 6 H), 3.35 (sept, 1 H, *J* = 6.5 Hz), 6.65 (dd, 1 H, *J* = 8.24, 2.44 Hz), 6.87 (d, 1 H, *J* = 2.44 Hz), 7.36 (d, 1 H, *J* = 8.24 Hz); MS *m/e* 201 (47), 161 (37), 159 (100), 124 (51), 123 (27), 114 (11); HRMS found 201.0384, calcd 201.0376). The analytical and spectral data, including HRGC retention time, of this product matched perfectly those of an authentic sample prepared from 3,4-dichloronitrobenzene by treatment with *i*-PrSNa to effect nucleophilic substitution of the activated *p*-chloro substituent followed by Sn/HCl reduction to the anilino derivative. The isomeric derivative 2-amino-4-chloro-1-[(1-methylethyl)thio]benzene, prepared via the same reaction sequence from 2,5-dichloronitrobenzene, was clearly distinguishable from **4** on the basis of GC retention time and ^{1}H NMR analysis.

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Registry No. **1a,** 88-73-3; **1b,** 100-00-5; RSNa (R = Me), 5188-07-8; RSNa (R = *i*-Pr), 20607-43-6; RSNa (R = *t*-Bu), 29364-29-2; RSNa (R = Ph), 930-69-8; *m*-chloronitrobenzene, 121-73-3; *o*-iodonitrobenzene, 609-73-4.

Supplementary Material Available: ^{1}H NMR spectra of compounds **3–6** (4 pages). Ordering information is given on any current masthead page.

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